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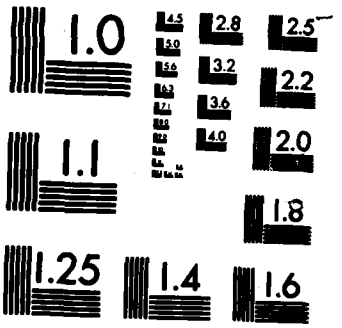

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CARDIO-PULMONARY RESPONSE TO SHOCK

ANNUAL AND FINAL REPORT

Herbert B. Hechtman, M.D.

September 30, 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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ABSTRACT

The general objectives of this laboratory have been to study cardiopulmonary abnormalities associated with shock and trauma, with a focus on the intermediary role of lung and circulating blood cell metabolism. Pressure breathing, pulmonary embolism and acid aspiration, by altering arachidonic acid metabolism were found to depress cardiac contractility and alter the distribution of systemic blood flow. The roles of prostacyclin (PGI2) and thromboxane (Tx) A2 in these settings were quantitated by radioimmunoassay and use of selective antagonists. These same prostanoids, along with platelet serotonin, also moderated changes in pulmonary function, particularly physiologic shunt, physiologic dead space and pulmonary vascular resistance. The secondary consequence of injury, the recruitment of an inflammatory reaction, was found to be a significant determinant of increased microvascular permeability both in acid injury of the lungs and heat injury to the skin. In both instances, neutrophil accumulations and permeability edema could be attenuated by inhibition of Tx synthesis. These data indicate that the prostanoids exert direct and indirect actions in moderating cardiopulmonary function following injury.

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

Studies for the past five years have been focused on cardiopulmonary abnormalities associated with shock, hemorrhage and trauma.

Pressure breathing and particularly positive end-expiratory pressure (PEEP) were found to alter pulmonary metabolic activities. In animals treated with PEEP: there was release of a humoral agent which decreased contractility; plasminogen activator normally cleared by the lungs during spontaneous breathing was now secreted; there was a decreased ability to clear barbiturates and lactate; a selective red cell acidosis was induced (during lactate infusion); and systemic blood flow was redistributed. Metabolism was severely altered when a lung lobe was isolated and perfused from a support dog. A variety of negative inotropic agents were released which led to death of the support animal. These cardiac muscle studies were assisted by the development of a new, isolated papillary muscle chamber.

Pressure breathing and particularly PEEP was also found to induce the pulmonary production of prostaglandins (PG). These PG regulate cardiac contractility and the release of plasmin mediated fibrinolytic activity. A high molecular weight protein has been tentatively identified as the circulating negative inotropic agent whose production is stimulated by PG synthesis during PEEP.

The large amount of prostacyclin (PGI_2) secreted by the lungs in response to surgery may protect against microaggregate entrapment and damage of the lungs. PGI_2 infusion was effective therapy for experimental pulmonary embolism.

Investigations continued into the relationship of pulmonary PG production and systemic organ function. Our study preparations were of pulmonary embolism and/or PEEP which we believe to be analagous to the microembolism and hyperventilation of severe injury. Both embolism and PEEP led to the production of thromboxanes (Tx) as well as decrease in cardiac contractility. The latter event could be prevented with Tx antagonists. Tx caused the elaboration of a high molecular weight protein fraction which suppressed myocardial Ca^{++}-ATPase and reduced activity of Krebs cycle enzymes in cardiac mitochondria.

During acute thrombocytopenia, serotonin (5-HT) infusion was found to protect against petechiae. Antagonists to 5-HT promoted petechiae. Endogenous or exogenously infused PGI_2 caused a reduction in plasma and increase in platelet 5-HT. Endothelial 5-HT transport was blocked. These findings may underly the ability of PGI_2 to enhance permeability.

Prostacyclin was found to regulate the production of plasminogen activator. This may be one of the mechanisms related to the dramatic effectiveness of PGI_2 in reversing the cardiopulmonary abnormalities of pulmonary embolism and in reversing lethal endotoxemia. However, PGI_2 was without benefit in treating acid aspiration, whereas blocking the proaggregatory prostanoid, TxA_2, effectively reversed the

pulmonary edema and the gas exchange abnormalities. Under other circumstances PGI_2 may be hazardous such as during organ perfusion. These studies indicate that PG are important mediators of critical illness, although their actions may not be predictable.

Our major hypothesis that platelet and white blood cell (WBC) secretions modify cardiopulmonary function has undergone further scrutiny. Particular attention has been paid to the role of arachidonic acid derivatives. Several common events have been found which stimulate the production of Tx such as exposure of blood to foreign surfaces, PEEP ventilation and pulmonary embolism. The release of TxA_2 was associated with the formation of a circulating substance which caused a decrease in contractility and abnormalities in myocardial ATPase. Prostacyclin has been found to be produced in large quantity following surgical trauma. Under these circumstances, endogenous PGI_2 increased cardiac output and dilated the systemic vasculature. An infusion of PGI_2 in an experimental setting of severe cardiac depression induced by endotoxemia led to rapid improvement of cardiac function. Unfortunately, PGI_2 also had adverse effects and paradoxically stimulates the production of TxA_2 in settings where blood is exposed to artificial surfaces.

Several experimental preparations have been used to study permeability edema. TxA_2 is centrally involved in the edema of acid aspiration, complement activation and burns. Leukotrienes (LT) are also of importance in the biochemical sequence which leads to capillary damage. We have also evaluated the vasoactive agent 5-HT as a potential culprit in the induction of respiratory failure without pulmonary edema. It was found that platelet entrapment in the lungs with 5-HT release can account for the increase in pulmonary vascular resistance, bronchoconstriction and hypoxia noted in acute respiratory failure prior to edema formation.

Edema following burn injury was due to WBC invasion and secretion of permeability factors related to arachidonic acid metabolism. This study was designed to test the ability of TxA_2 synthetase inhibitors and a LT receptor antagonist to modify burn edema. Four standard 2 cm^2 burns (100°C for 2 s) were produced on the backs of 400 g to 450 g rats at intervals of ½ h to 1 h. Evans blue dye (5 mg IV) was injected ½ h prior to sacrifice, at which time the burns were 3 h, 2 h, 1 h and ½ h old. In controls ($n = 9$) water content of unburnt skin was 67.6 ± 0.4% ($x \pm SE$). This rose to 73.2 ± 0.9% ½ h after burning; 71.7 ± 0.9% after 1 h; 71.9 ± 0.8% after 2 h; and 77.7 ± 0.6% after 3 h. Imidazole (25 mg/kg IV bolus) ($n = 8$) given 1½ h and ½ h after the "3 h" and "2 h" burns without effect; however, compared to untreated controls it did reduce blue dye accumulation and edema in the subsequent burns, inflicted ½ h and 1 h after drug administration ($p < 0.05$). Another Tx inhibitor, a pyridine derivative, (OKY 1555, 2 mg/kg IV bolus) ($n = 11$) was given at the same time as imidazole. It not only prevented edema formation in the skin burned 1 h after the

drug was administered (66.4 ± 1.4%, $p < 0.05$), but compared to untreated controls reduced edema to 71.0 ± 0.5% and 68.9 ± 0.7% in the skin burned 1 h and ½ h before drug therapy ($p < 0.05$). All burns showed reduced bluing. The LT antagonist (FPL 55712, 1.5 mg/kg IV bolus) ($n = 5$) compared to untreated controls reduced edema and bluing of the skin burned 1 h before therapy (72.8 ± 0.9%, $p < 0.05$) and prevented edema of skin burned after therapy (69.6 ± 1.4%, $p < 0.05$). These results indicate that TxA_2 inhibition can both prevent and treat burn permeability edema, an event mediated at least in part by LT.

Pulmonary arterial vasoconstriction mediated by platelet 5-HT was believed to be an important determinant of the increase in mean pulmonary arterial pressure (MPAP) after embolization. Using ^{99m}technetium-macro- aggregated albumin (Tc-MAA) perfusion lung scans, we examined the effects of ketanserin, a specific 5-HT receptor inhibitor on the cross-sectional area of the pulmonary vascular bed after experimental embolism. Five mongrel dogs were injected with 0.75 g/kg autologous clot. After 30 min MPAP had risen from 17 ± 2 mm to 43 ± 4 mm Hg (x ± SE). Multiple perfusion defects were noted on the initial low dose (600 uCi) Tc-MAA scan. Ketanserin, 0.15 mg/kg IV bolus, led to a fall after 30 min in MPAP to 27 ± 7 mm Hg ($p < 0.05$) and resolution of perfusion defects on a second high dose (12 uCi) Tc-MAA scan. There was no change in cardiac output. Computer subtraction of the high and low dose scans showed an increase of 12.0 ± 5.1% ($p < 0.02$) in perfusing lung areas after ketanserin, but not in untreated controls, reflecting vascular recruitment. Calculation of the expected increase in pulmonary vasculature cross-sectional area to explain the fall in MPAP according to Poiseuille's Law showed an increase of 21%; hence, the change in pulmonary vascular resistance mediated by 5-HT inhibition by both vascular recruitment and distention.

Acid aspiration leads to the pulmonary entrapment of platelets and WBC. We speculate that Tx produced by these cells leads to lung permeability and diminished cardiac performance. Twelve dogs were aspirated with 0.1 N HCl, 3 ml/kg. Within 30 min in untreated controls ($n = 6$); cardiac index (CI) decreased from 121 ml/min.kg to 104 ml/min.kg ($p < 0.05$); mean arterial pressure (MAP) fell from 142 mm Hg to 120 mm Hg ($p < 0.05$); PaO_2 fell from 91 mm Hg to 73 mm Hg ($p < 0.05$); while TxB_2 levels increased from 70 pg/ml to 130 pg/ml ($p < 0.05$). At 1 h, plasma was used to bathe a rat papillary muscle, and in comparison to pre-aspiration plasma led to a 10% decline in developed tension (Tpd) ($p < 0.05$). Transpulmonary WBC sequestration occurred after 2 h, while at 2.5 h edema fluid was noted in the endotracheal tube. Treated dogs ($n = 6$) received an infusion of the imidazole derivative ketoconazole 1 h after aspiration (2.5 mg/kg bolus followed by 10 mg/kg.h for 2 h). After 30 min of treatment: CI rose from 106 ml/min.kg to 143 ml/min·kg ($p < 0.05$); MAP rose from 128 mm Hg to 137 mm Hg ($p < 0.05$); PaO_2

rose and remained 20 mm Hg higher than controls ($p < 0.05$); TxB_2 fell from 130 pg/ml to 70 pg/ml ($p < 0.05$). At 2.5 h after aspiration plasma from treated animals in comparison to untreated controls led to a 8% higher Tpd ($p < 0.05$). Sequestration of WBC was not observed. After 4 h, 24 ml endotracheal edema fluid was collected in contrast to 127 ml in controls ($p < 0.05$). The importance of WBC Tx synthesis in the induction of permeability was tested by stimulating isolated WBC with the calcium ionophore A23187 in the presence or absence of 10^{-6}M ketoconazole. Ketoconazole reduced the number of leakage sites in the hamster cheek pouch from 196/cm^2 noted in controls to 28/cm^2 ($p < 0.05$). These data demonstrate that Tx directly or indirectly lead to cardiac depression and WBC mediated permeability.

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